

CLAIMS

WHAT IS CLAIMED IS:

1. An agonist antibody, fragment, or variant thereof which binds to a thrombopoietin receptor.
2. The antibody of Claim 1, wherein the thrombopoietin receptor comprises mammalian c-mpl.
- 5 3. The antibody of Claim 2, wherein the antibody stimulates proliferation, differentiation or growth of megakaryocytes.
4. The antibody of Claim 2, wherein the antibody stimulates megakaryocytes to produce platelets.
5. The antibody of Claim 2, wherein the thrombopoietin receptor is human c-mpl.
- 10 6. The antibody of Claim 2, which is selected from the group consisting of ScFv, Fab, F(ab')2 and IgG.
7. The antibody of Claim 2, which is a human antibody.
8. The antibody of Claim 2, which is a non-naturally occurring antibody.
9. The antibody of Claim 1, which is selected from the group consisting of 12E10, 12B5, 10F6 and 12D5.
- 15 10. The antibody of Claim 1, which is selected from the group consisting of Ab1, Ab2, Ab3, Ab4, Ab5 and Ab6, wherein each Ab1-Ab6 comprises a VH and VL chain, each VH and VL chain comprising CDR amino acid sequences designated CDR1, CDR2 and CDR3 separated by framework amino acid sequences, the amino acid sequence of each CDR in each VH and VL chain of Ab1-Ab6 selected according to the following table:

20	Ab1:	VH CDR1 (SEQ ID NO: 1) (SEQ ID NO: 2)	VH CDR 2 (SEQ ID NO: 3) (SEQ ID NO: 4)	VH CDR3 (SEQ ID No: 5) (SEQ ID No: 6)
		VL CDR1 (SEQ ID NO: 7) (SEQ ID NO: 8)	VL CDR2 (SEQ ID NO: 9) (SEQ ID NO: 10)	VL CDR3 (SEQ ID No: 11) (SEQ ID No: 12)
		Ab2:	VH CDR1 (SEQ ID NO: 13) (SEQ ID NO: 14)	VH CDR2 (SEQ ID NO: 15) (SEQ ID NO: 16)
25		VL CDR1 (SEQ ID NO: 19) (SEQ ID NO: 20)	VL CDR2 (SEQ ID NO: 21) (SEQ ID NO: 22)	VL CDR3 (SEQ ID No: 23) (SEQ ID No: 24)
		Ab3:	VH CDR1 (SEQ ID NO: 25) (SEQ ID NO: 26)	VH CDR2 (SEQ ID NO: 27) (SEQ ID NO: 28)
				VH CDR3 (SEQ ID No: 29) (SEQ ID No: 30)

	VL CDR1 (SEQ ID NO: 19) (SEQ ID NO: 20)	VL CDR2 (SEQ ID NO: 21) (SEQ ID NO: 22)	VL CDR3 (SEQ ID NO: 23) (SEQ ID NO: 24)
5	Ab4: VL CDR1 (SEQ ID NO: 25) (SEQ ID NO: 26)	VH CDR2 (SEQ ID NO: 31) (SEQ ID NO: 32)	VH CDR3 (SEQ ID NO: 33) (SEQ ID NO: 34)
10	VL CDR1 (SEQ ID NO: 35) (SEQ ID NO: 20)	VL CDR2 (SEQ ID NO: 21) (SEQ ID NO: 22)	VL CDR3 (SEQ ID NO: 23) (SEQ ID NO: 24)
15	Ab5: VH CDR1 (SEQ ID NO: 36) (SEQ ID NO: 37)	VH CDR2 (SEQ ID NO: 38) (SEQ ID NO: 39)	VH CDR3 (SEQ ID NO: 40) (SEQ ID NO: 41)
20	VL CDR1 (SEQ ID NO: 19) (SEQ ID NO: 20)	VL CDR2 (SEQ ID NO: 21) (SEQ ID NO: 22)	VL CDR3 (SEQ ID NO: 23) (SEQ ID NO: 24)
25	Ab6: VH CDR1 (SEQ ID NO: 42) (SEQ ID NO: 43)	VH CDR2 (SEQ ID NO: 44) (SEQ ID NO: 45)	VH CDR3 (SEQ ID NO: 46) (SEQ ID NO: 47)
30	VL CDR1 (SEQ ID NO: 48) (SEQ ID NO: 49)	VL CDR2 (SEQ ID NO: 50) (SEQ ID NO: 51)	VL CDR3 (SEQ ID NO: 52) (SEQ ID NO: 53).
35	11. The antibody of Claim 2, which does not stimulate megakaryocytes to produce platelets. 12. The antibody of Claim 1, having a detectable label. 13. The antibody of Claim 1, which is a monoclonal antibody. 14. The antibody of Claim 1, which is a single chain antibody. 15. The antibody of Claim 2, which is a mammalian c-mpl binding fragment. 16. An antibody immobilized on an insoluble matrix, wherein the antibody is the antibody of Claim 1. 17. A composition, comprising the antibody or fragment thereof of Claim 1 and a pharmaceutically acceptable carrier.		

18. The composition of Claim 17, which is sterile.

19. The composition of Claim 17, which is lyophilized.

20. A library of different single chain antibodies, comprising a plurality of the antibody of Claim 14.

5 21. The library of Claim 20, wherein the single chain antibodies are displayed on phage.

22. The library of Claim 21, wherein the phage is M13 and the antibodies are displayed as fusions of coat protein 3.

23. The library of Claim 22, wherein less than 20% of the phage display more than one fusion on the surface thereof.

10 24. A phage displaying on the surface thereof, the antibody of Claim 14.

25. The phage of Claim 24, wherein the phage is M13 and the antibodies are displayed as fusions of coat protein 3.

26. The phage of Claim 25, wherein the phage displays only one fusion on the surface thereof.

15 27. A fusion protein, comprising at least a portion of a phage coat protein fused at the amino terminus thereof to the antibody of Claim 1.

28. The fusion protein of Claim 27, wherein the phage coat protein is M13 coat protein 3.

29. A method of stimulating proliferation, differentiation or growth of megakaryocytes, comprising contacting megakaryocytes with an effective amount of the antibody of Claim 1.

30. The method of Claim 29, comprising administering the antibody of Claim 1 to a patient in need thereof.

20 31. A method of increasing platelet production, comprising contacting megakaryocytes with an effective amount of the antibody of Claim 1.

32. The method of Claim 31, comprising administering the antibody of Claim 1 to a patient in need thereof.

25 33. Isolated nucleic acid encoding the antibody of Claim 1.

34. A vector comprising the nucleic acid of Claim 33.

35. A host cell comprising the vector of Claim 34.

36. A method of producing an agonist antibody comprising culturing the cell of Claim 35 under conditions wherein the nucleic acid is expressed.

30 37. An agonist antibody, fragment or variant thereof which binds to a MuSK receptor.

38. A method of activating a receptor protein having two sub-units, comprising contacting the receptor with a single chain antibody which binds to the receptor.

39. The method of Claim 38, wherein the receptor is a tyrosine kinase receptor.

40. The method of Claim 38, wherein the receptor is a cytokine receptor.

35 41. A method of improving neuromuscular function in a patient in need thereof and expressing MuSK receptor, comprising administering to the patient an effective amount of the antibody of Claim 37.

42. The method of Claim 38, wherein the single chain antibody is expressed as a human IgG.

Add A1

Add B2